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LIVER

Modified interferon γ targets key cells responsible for liver fibrogenesis

The cytokine interferon (IFN)-γ has potent antifibrogenic properties *in vitro*. However, this molecule has proven disappointing in clinical trials; one of the reasons for this is that off-target effects are common owing to the presence of IFN-γ receptors on nearly all cell types. Ruchi Bansal and colleagues have investigated a method to target IFN-γ to hepatic stellate cells (HSCs), which are the key cells responsible for liver fibrogenesis.

"In the past, our group has developed a cyclic peptide that has specific affinity for platelet-derived growth factor beta receptor (PDGFβR)," explains Bansal. "To target IFN-γ to HSCs, we used our PDGFβR recognizing peptide ... as PDGFβR is highly over-expressed in activated HSCs in liver fibrosis." The group conjugated IFN-γ to this cyclic peptide and analyzed the biological activity and the PDGFβR binding specificity of these constructs using *in vitro* and *in vivo* models.

The modified IFN-γ constructs were found to retain their biological activity and showed PDGFβR-specific binding to fibroblasts and HSCs *in vitro*. The *in vivo* model demonstrated that modified IFN-γ inhibited HSC activation and attenuated liver fibrosis. Furthermore, adverse affects were reduced or absent compared with unmodified IFN-γ.

"Further studies will be undertaken to examine the therapeutic and adverse effects of these constructs in other animal models of liver fibrosis," concludes Bansal. "Parallel to these proof-of-concept studies, a preclinical research program has been set up in coordination with experts in the field to prepare for clinical trials."

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Original article Bansal, R. *et al.* A novel engineered targeted interferon gamma blocks hepatic fibrogenesis in mice. *Hepatology* doi:10.1002/hep.24395